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Review

Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health

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ABSTRACT

CT-P13, the biosimilar of infliximab, has been recently approved in the EU, Australia, Canada, Japan and many other countries. Thus, it was the first biosimilar approved in the field of rheumatology, dermatology and gastroenterology. Since there has been debate about the issue of switching from RMP to the biosimilar and some national societies have expressed concerns, this review was written with the following objectives:

- Review the data evaluating the safety and effectiveness of switching to CT-P13 accumulated thus far from clinical studies and real-world experience.
- Assess the paradigm shift around the use of biosimilar products in terms of recent national decisions and stakeholder perspectives.

The review concludes that whilst prudent switching practices should be employed, growing safety experience accumulated thus far with CT-P13 and other biosimilars is favorable and does not raise any specific concerns.

1. Introduction

Biological agents have revolutionized therapy and transformed treatment paradigms due to improved short- and long-term clinical and public health outcomes, and general patient care of chronic and debilitating autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps) and psoriatic arthritis (PsA), ulcerative colitis (UC) and Crohn's Disease (CD) as well as for different forms of cancer and chronic kidney disease. However, with global spending on medicines approaching to reach $1.3 trillion by 2018 (IMS, 2014), colossal costs of biological treatments reaching $210 billion by 2016 (IMS, 2012) with relatively low numbers of patients being treated or assured access globally to these efficient treatments, long-term expenditure and costs has become unsustainable for payers and societies. Recent or impending expiry of patents for some key biologics has led to development of biosimilar products. With growing numbers of biosimilar products there are now more options for healthcare providers and patients not only to access biological products earlier but also to possibly switch from costly originator versions to biosimilar alternatives. The entry of biosimilar products into the market may well reduce the pressure on healthcare budgets, increase earlier access to biologic therapy, and may facilitate the efficient allocation of limited financial resources [1,2]. Biosimilars are expected to save 11.8–33.4 billion Euros between 2007 and 2020 in the EU and 44.2 billion US dollars over the 10 year period between 2014 and 2024 [3,4].

In accordance with regulatory frameworks laid out by the European Medicines Agency (EMA), the US Food & Drug Administration (FDA), the World Health Organization (WHO) and other authorities in highly regulated jurisdictions, development of biosimilars has to be accomplished by rigorous and comprehensive comparability exercises in order to assure similarity of the biosimilar with the reference medicinal product (RMP) in terms of quality characteristics, biological activity, safety, efficacy [5] including the absence of any clinically important differences from the RMP in terms of safety and effectiveness [6]. The EMA has pioneered the legal, regulatory and scientific framework for

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approval of biosimilars with 20 products approved between 2006 and 2015, while other assessments of biosimilar products are ongoing. The WHO enacted biosimilar guidelines in 2009 and its framework has been put forward into regional and national biosimilar legislation and allowed to strengthen global regulations of biosimilars [7].

The Biologics Price Competition and Innovation Act (BPCI Act) in the US has established an abbreviated approval pathway for biological products to demonstrate similar efficacy and safety with the RMP. The federal law has differentiated the approval of products into two stages: (1) the 'biosimilar' has to provide evidence of basic similarity to the RMP, and (2) an additional approval status called 'interchangeable biosimilar' is required to allow for unlimited transition from the RMP.

As indicated in Public Health Act subsection 351(k) (3), a biosimilar is considered to be interchangeable with the reference product if:

- the biological product is biosimilar to the reference product, and
- it can be expected to produce the same clinical result in any given patient.

In addition, for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar and the reference product is not greater than the risk of using the reference product without such switching or alternating.

Biosimilarity therefore does not imply interchangeability which is much more stringent. Interchangeability status allows substitution of RMP with biosimilar without healthcare provider involvement. In addition to interchangeability, there is a concept of switching between an RMP and its biosimilars. Switching can be carried out either under consent of healthcare provider or without such consent but following payer's policy or decision only (automatic substitution) [8].

The approval for interchangeability is rigorous to achieve and FDA demands to establish safety data clearly showing that no additional risk is incurred when patients are switched to the biosimilar as compared to the continuous use of the RMP [9]. Interchangeability refers to achievement of same clinical result in any given patient in terms of quality, safety and efficacy when a biosimilar is switched or substituted with its respective innovator biological product, when compared to the use of the reference product alone. In principle, once the biosimilar product gains 'interchangeable' status, it can be automatically substituted for the prescribed biological product by the pharmacist without consent of the prescribing physician [9]. However, this provision is subject to U.S. state laws enforcing substitution legislation. The BPCI Act gives FDA the authority to designate a biosimilar as interchangeable with its reference product. This means that the biosimilar may be substituted for the originator product by the pharmacist without reference to the prescribing physician. FDA unveiled biosimilar guidelines in 2012 and in January 2015 approved first US-approved biosimilar, Sandoz's Zarxio™ (filgrastim-sndz) [10]. However, as of 2015 there are no interchangeable biosimilars approved in the USA. Despite that the concept of interchangeability has been laid in BPCIA, the requirements and the data required to accomplish interchangeable status have not been clearly defined. After long-term debates no defined path, guidance and clear requirements were issued in the USA. FDA has yet to clarify the requirements for interchangeability, although the agency has stated that it highly recommends that sponsors use a two-step process for obtaining the interchangeable biologic designation, first gaining approval as a biosimilar and then submitting a supplement with new data to support interchangeability.

Recommendations around interchangeability and substitution between biosimilar and its RMP are not within the remit of EMA but reside with EU member national authorities [11,12]. Recently some national agencies in the EU experts issued their position statements welcoming switching to biosimilar products and raising concerns over the scientific purpose, feasibility, utility and usefulness of over-complex and often unsurmountable interchangeability requirements and how these fit with economically sustainable placement of these products onto the market [13–19].

Following approval of biosimilars, it is important to decide whether it is possible to alternate or switch from the originator product to the biosimilar or vice versa in clinical practice or also to switch between different biosimilars. However, concepts of interchangeability and switcheability have been insufficiently studied - not only in context of biosimilars but also with originator biologics in general. Switching from one therapy to another one has been an integral part of medical practice. Indeed, switching can possibly occur between small molecule drugs, branded and generic synthetic medicines, between synthetic agents in biological agents and also from one type of biological originator agent (e.g. anti-tumor necrosis factor (TNF) agent) to a biological product from a different class (e.g. rituximab). However, switching studies have never been routinely conducted and sequencing of agents or their positioning in treatment paradigm was largely based on empirical evidence or limited clinical trial data. Strategy studies such as TICORA and BEST have provided some evidence that earlier initiation and more intensive treatment and whenever appropriate switching to other more potent synthetic disease-modifying antirheumatic drugs (DMARD) resulted in better control of disease activity in RA patients and improved clinical outcomes at no additional cost for healthcare [20,21].

Therefore, it is important to recognize that switching may become necessary for numerous reasons which can be broadly categorized into the following groups:

- Loss of response of effectiveness of the primary agent;
- Safety concerns including adverse events or immunogenicity;
- Adherence and compliance related factors (e.g. more convenient route, frequency of administration, palatable oral formulation etc.);
- Healthcare provider induced switching that can take place in form of automatic substitution under budgetary or cost-effectiveness considerations.
- Other considerations that could be prompted by both pharmacists and patients, e.g. longer product half-life and stability, lesser cold-chain requirements, etc.

CT-P13, the biosimilar of infliximab, has been recently approved in the EU, Australia, Canada, Japan and many other countries. Thus, it was the first biosimilar approved in the field of rheumatology, dermatology and gastroenterology. Since there has been debate about the issue of switching from RMP to the biosimilar and some national societies have expressed concerns, we decided to write this paper with the objectives to review switching experience between RMPs and their biosimilar versions and principles around switching to biosimilar products could assure both safe and economically sustainable use of these products.

2. Original experience with switches between different biological products

Sequencing of patients with autoimmune diseases through different lines of immunomodulatory therapies is a cornerstone approach of clinical practice and is outlined in recommendations of EULAR, ECCO and other bodies [22–24]. The typical approach is to

introduce a conventional non-biologic DMARD first, followed by combination non-biologic DMARDs or biologics in non-responders. The initial biologic used in the vast majority of patients is typically anti-TNF agent. In clinical trials there is usually a wash-out period and no randomized controlled studies have been conducted to assess the safety and effectiveness of switching between biological products and mostly the original experiences were learned from various registries and observational studies. These studies yielded controversial data probably due to various confounding factors and lack of concurrent free drug concentration and anti-drug formation monitoring.

The SWITCH study in CD patients evaluated switching stable patients on infliximab maintenance patients to adalimumab and found loss of tolerance to adalimumab and high proportion of discontinuations [25]. Other studies showed that there may be benefits of switching AS patients between unrelated anti-TNF agents [26] and also that immunogenicity to infliximab or adalimumab may reduce the probability of achieving response in RA or PsA patients to etanercept or other alternative second anti-TNF agent [27–32]. Changing the mechanism of action has been advantageous in comparisons of rituximab and abatacept versus a subsequent anti-TNF as demonstrated by improvements in RA disease activity as well as persistence of therapy [33–37]. There is need to generate more clinical data ideally derived from randomized controlled studies or pragmatic studies to determine merits of switching between originator anti-TNF products. One of such studies in RA has recently been initiated [38].

3. Biosimilars: evaluation of immunogenicity

Development of biosimilar candidates is reliant on a comprehensive and rigorous analytical comparability exercise which is aimed to establish highly similar structural and functional features. Over last decade EMA has developed a well-refined biosimilar pathway and now accumulated experience with approval of 21 products belonging to different classes of recombinant proteins including two brands of biosimilar infliximab (CT-P13, Remsima®, Celltrion and Inflectra®, Hospira) and more recently biosimilar etanercept. Global approvals of CT-P13 illustrate that it is possible to accomplish successful development of a biosimilar monoclonal antibody despite of the given complexity of analytical, functional and clinical studies.

In a range of approved indications with reference products there are often significant differences in use of background immunomodulatory and/or chemotherapy regimens, the degree of immunocompetence and patient related factors, doses and dosing schedules. Therefore susceptibility of a different patient population to product-related toxicity and immunogenicity may vary. Biosimilar sponsors should provide robust scientific justification for extrapolation of indications. This justification is based on the both biosimilarity data and the prior data with RMP. There is continuously growing experience with extrapolation of indications with approved biosimilar products that support the foundation of this scientific and regulatory approach [39].

The choice of the patient population for the comparability indication should take into account the evaluation of immunogenicity accounting for product and patient specific factors and concomitant use of immunomodulatory therapies [40,41].

As monotherapy, infliximab and adalimumab are the most immunogenic of the available anti-TNF MABs, and anti-drug antibodies (ADA) were reported in approximately 50–61% with CD and RA [42,43]. High-dose tolerance is a well-known immunologic phenomenon and appears to explain the inverse dose–response in immunogenicity of TNF antagonists, as has been shown for infliximab, which was progressively less immunogenic at 1, 3 and 10 mg/kg [42]. In addition, concomitant use of methotrexate (MTX) can reduce the probability of ADA formation [42,44,45]. However some studies in RA patients treated with 3 mg/kg of infliximab found anti-infliximab antibodies in >40% of the patients, despite concomitant MTX treatment [46]. The PLANET-RA study with biosimilar infliximab CT-P13 has illustrated that up to 50% of patients concomitantly treated with MTX developed anti-ADA [47,48]. Accordingly, intra-study evaluation of immunogenicity under single or multiple-dosing and using appropriately validated methods is the most adequate approach. Regardless of how sensitive and compelling pre-licensure immunogenicity data might be, the rarity of some of some serious events such as pure-red cell aplasia does not allow adequately capture these in pre-marketing circumstances and demand well-designed post-marketing registries and observational studies. Of note in the EU experience with biosimilar erythropoietins (EPOs) the burden or PRCA events was negligibly lower compared to the reports with the reference product [49]. Evaluation of the nature of ADA (e.g. neutralizing vs non-neutralizing) and magnitude of immune response in relation can assist in understanding of the immunogenicity risk and determining the clinical relevance of the anti-drug immune response.

Some *in vitro* studies including disease specific *in vitro* experiments or *in silico* or *in vitro* predictive immunogenicity models are very likely to play an increasing role by replacing the need for large pre-marketing databases and providing with some additional extrapolation licensure support. Until recently some of these predictive methods were in early stage of validation and had numerous limitations [50]. However, more recently some of these assays were reported to predict the immunogenicity risk with some non-sequence related post-translational modifications increasing the breadth of their potential use for *in vitro* comparative assessment of immunogenicity. For example, effects of non-sequence derived post-translational modifications including those of a biophysical or biochemical nature such as deimination (or citrullination), deamidation, oxidation, dimerization, and protein folding-induced conformational changes including stress and stability related aggregation that are all widely accepted as determinants of immunogenicity can be now reliably evaluated and predicted using various *in silico* and *in vitro* assays [51].

In vitro cross-immunogenicity study comparing CT-P13 and infliximab RMP using sera from CD patients who developed anti-infliximab RMP antibodies has demonstrated high similarity in binding illustrating similar immunogenicity and presence of the shared immunodominant epitopes in CT-P13 and infliximab RMP sequences. In addition, anti-adalimumab antibodies did not cross-react with CT-P13 or infliximab RMP [52]. Therefore *in vitro* studies can be useful in assessment of immunogenicity of biosimilar products and some of these *in vitro* studies can be also tailored to assessment of switch-related immunogenicity risks. Throughout last two decades an effort in MAB “humanization” translated in lowering of the incidence of ADA with reference products and given a rarity of immunogenicity with some products and its inconsistent relationship with the risk of infusion related reactions, the emphasis should be on development of both routine and enhanced post-marketing surveillance of the product and risk management planning [53]. As we are moving forward from chimeric products associated with greater immunogenicity risks into development of biosimilars of more humanized versions of reference products, and given inherent limitations of clinical models and much greater fidelity of powerful and extremely sensitive state-of-art analytical techniques, the paradigm of both biosimilarity and extrapolation should aim to shift into analytical continuum of comparability and obviate the need for clinical studies [54]. With strengthened and pro-active pharmacovigilance systems available in well-developed and regulated markets, the

extrapolation should be further supported by systematic and comprehensive safety and immunogenicity evaluation across all indications through pro-active post-marketing surveillance of well traceable biosimilar products. New pharmacovigilance legislation instituted by EMA in 2012 has been welcomed since it provided with focus on performance and effectiveness of risk minimization activities [53,55]. Instead of routine passive surveillance, post-approval registries and safety studies are expected from developers of complex biosimilars and these are aimed to complement an absence or a shortfall in pre-licensure safety databases with post-marketing evaluation of rare adverse events or addressing the missing clinical data in extrapolated indications [53].

4. A decade of safety experience with biosimilars and switching in the EU

A substantial and positive effectiveness and safety experience in the EU has been accomplished with biosimilar products over last decade through Eudravigilance and from stakeholders and payer perspectives [39,56,57]. In all cases of approved biosimilars extrapolation principle has been claimed and employed as justified by applicants using a totality of generated biosimilarity dataset and review of mechanistic and pathophysiological differences between conditions of use. Satisfactory safety experience of switching between primary generation of biosimilar filgrastims and EPOs has been validated by excellent traceability of adverse events and lack of any evidence of increase in unwanted safety, immunogenicity or altered effectiveness of the products under real-world scenario and tender systems employing these products throughout EU [39,57]. Substantial 10-year safety experience with biosimilar products in EU translates now into millions patient year exposures. Robust pharmacovigilance systems and post-marketing registries and studies are ongoing to further evaluate the safety profile and refine the understanding around real-world use, although the evidence from controlled studies is relatively limited [39,57].

Omnitrope® was the first EMA-approved recombinant hGH biosimilar in 2006. Through post-marketing studies and registries it was found that there is no negative impact on efficacy or unexpected adverse events after switching to omnitrope® from its RMP [58].

Eight biosimilar filgrastim products were approved by EMA since 2008. One of them, Zarxio™ was the first US approved biosimilar product. At the time of US approval, the global safety experience with this product encompassed >7 million patient years. Post-marketing studies confirmed efficacy and safety of biosimilar filgrastim products in the approved indications including the extrapolated indication of mobilization of stem cells in healthy donors and did not identify any concerns resulting from switching [59–62].

Five biosimilar EPOs were approved by the EMA [63,64]. Following approval, randomized, comparative switching studies have been conducted with these biosimilars in patients with chronic renal failure [65,66]. These studies demonstrated that there are highly comparable clinical efficacy and safety profiles between two patients group; switching to a biosimilar EPO or remaining on originator EPO. Non-randomized analyses also demonstrate that biosimilar EPOs and originator EPO can be interchanged without clinically meaningful alterations in efficacy or safety [67,68].

To investigate the differences between originator and biosimilar EPO utilization, Hörbrand et al. analyzed the database of the Bavarian statutory health insurance physician's association [69]. This study show that EPO consumption and persistence of patients on chronic hemodialysis based on defined daily doses is similar among patients receiving originator, biosimilar, or switched therapy (from originator to biosimilar or vice versa). This data provide with evidence that the persistence on biosimilar product is not affected following switching.

Recent meta-analysis and systematic review of post-marketing clinical studies and pharmacovigilance databases provides with assurance that the switching between EPOs, filgrastims and growth hormone biosimilar products do not raise any specific safety concerns including lack of concerns related to switching [70].

5. Clinical data and switching experience with biosimilar infliximab CT-P13

Infliximab is a human-murine chimeric monoclonal antibody against TNF and its biosimilar CT-P13 (Remsima®, Inflectra®) was approved by the EMA in 2013 as a first monoclonal antibody biosimilar. Biosimilarity between CT-P13 and its RMP was demonstrated by comprehensive physicochemical, non-clinical and clinical studies including two pivotal clinical studies [48,71,72]. Clinical program PLANET included a therapeutic equivalence PLANETRA study in 606 patients with RA on background of MTX that showed equivalent efficacy, comparable PK, immunogenicity and safety profiles of CT-P13 and RMP in RA patients at week 30. In additional large PK study PLANETAS, PK equivalence and comparable efficacy, immunogenicity and safety of CT-P13 and RMP in 250 AS patients at weeks 30 were demonstrated. AS study was conducted without background immunosuppressive therapies and illustrated similar immunogenicity profile to that of RMP up to 1 year. Japanese study in 108 Japanese RA patients on background of MTX demonstrated PK equivalence and comparable efficacy, safety and immunogenicity of CT-P13 and RMP [72].

Since launch of CT-P13 across EU and other regions post-marketing safety experience is rapidly growing. As of July 2015, the post-marketing exposure with CT-P13 for all approved indications across worldwide territories had accumulated to approximately 24,000 patient-years. There are various post-marketing registries and studies are ongoing to accumulate safety experiences with CT-P13. With regards to switching from originator infliximab to CT-P13, positive clinical evidence is being accumulated from several observational studies and real-world patient cohorts.

Extension studies of the PLANETRA and PLANETAS studies were performed to investigate the longer-term efficacy and safety of extended CT-P13 treatment over 2 years (maintenance group), and the efficacy and safety of switching from originator infliximab to CT-P13 for 1 year (switch group) (Table 1) [73–75].

In RA extension study, 302 patients who participated in 1 year PLANETRA study entered into the open-label extension phase for an additional 48 wks: 158 patients were maintained with CT-P13 (maintenance group) and 144 patients were switched from RMP to CT-P13. At wk 78, ACR20/50/70 response rate was comparable for the maintenance group (71.5%/48.3%/24.5%) and switch group (78.2%/47.9%/29.6%). Through wk 102, ACR20/50/70 response rates were maintained and were similar in each group; 72.2%/48.3%/24.5% and 71.8%/51.4%/26.1%, respectively. Good and moderate EULAR-CRP responses at wks 54, 78 and 102 were observed in 89.4%/79.5%/81.5% of pts in the maintenance group and 87.3%/85.9%/76.8% of pts in the switch group, respectively. Changes in DAS28-CRP from baseline were comparable between the two groups: −2.4/−2.4/−2.4 in the maintenance group; −2.4/−2.6/−2.5 in the switch group, at wks 54, 78 and 102 respectively). EULAR-ESR response rates and DAS28-ESR results were also comparable between groups. The proportion of ADA positive patients was comparable between the two groups throughout the study and ADA positivity did not increase significantly during year 2 when both groups were receiving CT-P13: maintenance group, 49.1%, 50.4%

Table 1
Randomized clinical trials and observational studies for switchability of CT-P13.

Country (study)	Patient numbers	Indication	Efficacy	Safety	Ref
16 countries (PLANETRA)	302 (maintenance group = 158, switch group = 144)	RA	Highly similar efficacy between maintenance and switch groups based on ACR 25/50/70, DAS28-ESR, DAS28-CRP, EULAR-ESR, and EULAR-CRP	Comparable immunogenicity and treatment-emergent adverse event profiles	[73]
8 countries (PLANETAS)	174 (maintenance group = 88, switch group = 86)	AS	Highly similar efficacy between maintenance and switch groups based on ASAS 20/40, ASAS partial remission rate, BASDAI, BASFI, BASMI and chest expansion	Comparable immunogenicity and generally comparable safety profiles	[74,75]
South Korea	110 (CD = 59: 32 infliximab-naïve, 27 switch), (UC = 51: 42 infliximab-naïve, 9 switched)	IBD	Naïve: - Response: 95.5% and 91.3% in CD and UC patients, respectively at week 30 - Remission: 77.3% and 47.8% in CD and UC patients at week 30 Switch: Efficacy of CT-P13 was maintained in 92.6% and 66.7% of CD and UC patients, respectively	AEs related to CT-P13 occurred in 11.8% of UC patients	[76]
South Korea	173 (CD = 83: 43 infliximab-naïve, 40 switch), (FCD = 12: 8 infliximab-naïve, 4 switch), (UC = 78: 62 infliximab-naïve, 16 switch).	IBD	Naïve: - Response: 79.5%, 66.7%, and 72.2% in CD, FCD, and UC patients, respectively at week 30 - Remission: 59.0%, 50%, and 37% in CD, FCD, and UC patients at week 30 Switch: 80.6%, 50%, and 45.5% of CD, FCD, and UC patients, respectively, achieved or maintained remission	No unexpected AEs, well-tolerated	[77]
South Korea	17 (CD = 8: 3 infliximab-naïve, 5 switch, (UC = 9: 5 infliximab-naïve, 4 switch)	IBD	Naïve: - Response & remission: 87.5% in IBD patients at week8 Switch: - 88.9% showed a similar clinical outcome compared with originator biologic	One UC patient experienced arthralgia	[78]
Poland	32 (switch)	Pediatric CD	Switch: - Response & remission: median PCDAI 48 (at start of RMP)→8.5 (at switch to CT-P13)→ 7.5 (at second CT-P13 infusion)	No unexpected AEs	[79]
Finland	39 (switch)	RA	Switch: - No statistical significant difference in terms of AUC for pain (VAS), fatigue, PtGlob, PtAct, HAQ, DrGlob, ESR, CRP at after CT-P13 injection for 11 months	No immediate safety signals were observed	[80]

and 46.4%; switch group, 49.3%, 49.6% and 49.6% at wk 54, 78 and 102, respectively. The frequencies of AEs and SAEs between maintenance and switched treatment groups were: 53.5% and 53.8% for AEs and 7.5% and 9.1% for SAEs, respectively. Infusion-related reactions were reported in 10 patients (6.3%) in the maintenance group and in 4 patients (2.8%) in the switch group. There were no reports of TB infections in either group. Malignancies were reported in 1 patient (ovarian cancer) in the maintenance group and in 4 patients (breast cancer, T-cell lymphoma, ovarian cancer and myeloproliferative disorder) in the switch group [73].

In a smaller AS extension study, a total of 174 patients who completed PLANETAS entered into the extension phase: 88 were continuously treated with CT-P13 (maintenance group) and 86 were switched from RMP to CT-P13 (switch group) for additional 48 weeks. During the extension, ASAS20/ASAS40 rates were similar in the maintenance group (70.1%/57.5% at wk 78 and 80.7%/63.9% at wk 102) and the switch group (77.1%/51.8% at wk 78 and 76.9%/61.5% at wk 102). ASAS partial remission rates were also similar between groups; 21.8% and 21.7% at wk 78, and 27.7% and 28.2% at wk 102, respectively. ADA rates were comparable between the two groups and positivity was maintained throughout the study (maintenance group, 22.2%, 24.4% and 25.0%; switch group, 26.2%, 31.3% and 30.7%, at wk 54, 78 and 102, respectively). As expected, ADA negative patients achieved higher ASAS40 responses (maintenance group, 62.9%/61.5%/66.1%; switch group, 58.1%/60.0%/71.2% at wks 54, 78 and 102, respectively) compared with ADA-positive patients (maintenance group, 38.9%/36.8%/55.0%; switch group, 41.7%/33.3%/45.8% at wks 54, 78 and 102, respectively) with no differences between the maintenance and switch groups. The proportion of patients with AEs was 48.9% in the maintenance compared with 71.4% in the switch group but there was no temporal or exposure related association between occurrence of AEs and switching. Most of AEs were mild and moderate in terms of severity. SAEs were reported in 4 patients in each treatment group. AEs due to hypersensitivity and infusion-related reactions were similar in both groups (5 patients in the maintenance group vs 2 patients in switch group). There was 1 case of TB in each group and 1 report of prostate cancer in the maintenance group [74,75].

Both RA and AS extension studies did not reveal any signs of altered efficacy, safety or immunogenicity profile following transition from RMP to CT-P13. The proportion of immunogenicity related safety events was similar between maintenance and switched AS and RA patients.

Up to date, there are five published observational studies including the patients switching from originator infliximab to CT-P13 (Table 1). Clinical efficacy and safety of CT-P13 were evaluated in 110 Korean IBD patients (CD = 59, UC = 51), including 36 patients (CD = 27, UC = 9) switching from originator infliximab to CT-P13 [74]. Clinical remission, response and safety profile of CT-P13 were comparable with the historical data of the originator infliximab in IBD patients. In patients who receive switched treatment from originator infliximab to CT-P13, the efficacy of CT-P13

was maintained in 92.6% and 66.7% of CD and UC patients, respectively. Satisfactory clinical efficacy and safety of CT-P13 were also confirmed in other observational studies from 173 (CD = 83, fistulizing CD [FCD] = 12, UC = 78) and 17 (CD = 8, UC = 9) Korean IBD patients, including 60 (CD = 40, FCD = 4, UC = 16) and 9 (CD = 5, UC = 4) switching patients, respectively [76,77]. Moreover, two observational studies including 32 paediatric CD and 39 RA patients who received switching therapy were also reported in Europe. In these studies, efficacy and safety were well maintained after switching [78–80].

Several registries and post-marketing studies are ongoing for evaluation of CT-P13 in several indications such as RA, AS, CD, UC, AS, Ps/PsA, and clinical outcomes following switching treatment from originator infliximab to CT-P13, will be accumulated and reported in these studies (Table 2). In addition, three randomized clinical trials including about 800 patients are ongoing for evaluating switchability of CT-P13.

With almost complete nationwide uptake of CT-P13 in Norway, Norwegian authorities have commissioned a clinical trial that is currently ongoing (NOR-SWITCH; ClinicalTrials.gov identifier NCT02148640). This is a randomized, double-blind trial to compare the safety and efficacy of continued originator infliximab treatment to switching from originator infliximab to CT-P13 in 500 patients with RA, spondyloarthritis (SpA), UC, CD and Ps. This clinical trial is carried out by Norwegian regional health trusts and fully funded by Norwegian government and expected to report results in 2016 [81].

Additional multicenter, randomized, double-blind clinical study have been initiated to assess safety and non-inferiority of efficacy of CT-P13 and original infliximab in adults with CD (NCT02096861). This study is conducted jointly by Celltrion and Hospira/Pfizer. In this study a randomized transition from originator infliximab to CT-P13 as well as from CT-P13 to originator infliximab will be evaluated.

An extension study in 71 Japanese RA patients evaluated the safety and efficacy of CT-P13 following a switch from original infliximab as well as the long-term safety and efficacy of CT-P13. This study showed consistent safety, immunogenicity and efficacy profile between maintenance and switch treatment groups [72].

In totality a large amount of clinical data is already available in patients with different forms of autoimmune diseases who were switched from RMP to CT-P13 with satisfactory outcomes, sustained efficacy and no sign of increased immunogenicity or any other safety concerns. Whilst most of this data is derived from observational cohorts and open-label studies, the role of "real-world" and pragmatic clinical studies and methods of collecting the evidence is increasingly becoming important. It is uncertain whether large and long-term longitudinal randomized controlled studies elucidating interchangeability are both feasible and practical. Therefore it is likely that many biosimilar sponsors will opt for real-world evidence gathering using observational studies, registries, databases and surveys.

In conclusion, through extension studies evaluating single-way transition from originator infliximab to CT-P13, initial observational cohort and studies in RA and IBD patients as well as through ongoing registries and randomized controlled studies an extensive safety, effectiveness and immunogenicity experience with switching to CT-P13 has been accumulated. The clinical data from these studies, post-marketing pharmacovigilance data and real-world observational clinical data provide with reassuring safety data in relation to switching. Thus far no safety or immunogenicity concerns have been raised. Experience with the use of CT-P13 is continuously growing with exposure reaching 24,000 patient-years treated worldwide.

6. Changing paradigm in relation to switching

Over last decade a number of learned societies issued their "position" statements challenging concepts of biosimilarity and extrapolation but also raising concerns over switching that may occur in real clinical practice [22,80–82]. A number of surveys indicate that there are concerns of some stakeholders in relation to switching due to potentially low educational level amongst prescribers concerning biosimilars [82–85].

Despite of these concerns the uptake of biosimilar products and the use of biosimilar infliximab are rapidly expanding across the globe without any risks emerging from switching thus far. A number of physicians who are passionate about improving patient access in countries where the very use of biological products was scarce have experienced switching under their care and are now actively collecting the data on the use of CT-P13 [86,87]. Understanding of safety of product substitution is particularly important in healthcare systems where under tender agreements the use of different and potentially multiple products may occur as a result of pricing competition.

To date, six regulatory authorities of different counties reported their stance on interchangeability or substitutability of biosimilars and RMPs, and all these authorities generally have positive views in relation to substitution (Table 3) [13–19]. Most recent position statements issued by Medicines Evaluation Board of Netherlands and Finnish Agency indicated that switching to biosimilars should be allowed [13,14]. More recently Australian (PBAC) reported that substitution of biosimilars and RMPs is allowed if the biosimilar is found to be equivalent in terms of efficacy and safety [17]. Paul-Ehrlich Institut in Germany has also issued a position statement regarding interchangeability of biosimilars and stated that decision on switching "must be based on scientific data, especially with regard to proven high-grade comparability of a biosimilar to its originator product and the scientific plausibility of all data included in the discussion" rather being based on arguments "with little foundation and fears in connection with the exchange of the

Table 2
Ongoing registries and post marketing studies for evaluation of CT-P13.

Study	Country	Patients number	Indication	Study type (ClinicalTrials.gov identifier)
NOR-SWITCH study	Norway	500	RA, SpA, PsA, UC, CD, and PsO	RCT (NCT02148640)
CD switching study	19 countries	214	CD	RCT (NCT02096861)
RA switching study	Japan	~100	RA	RCT
RA registry in Korea, EU	7 countries	2450	RA	Registry
IBD registry in Korea, EU	9 countries		IBD (CD,UC)	Registry
AS registry in Korea, EU	5 countries		AS	Registry
Post-marketing study in Korea	Korea	1600	RA, AS, IBD, PsA, PsO	Post-marketing Study
BSRBR	UK	500	RA	Registry
RABBIT	Germany	500	RA	Registry

RCT: Randomized clinical trial.
BSRBR: The British Society for Rheumatology Biologics Registers.
RABBIT: Rheumatoid Arthritis oBservation of BIologic Therapy.

Table 3
Stance of regulatory authorities on interchange and substitution of biosimilars

Regulatory authority	Interchange	Substitution	Ref
EU (EMA)	Leaving it to each member country to decide	Not permitted at the pharmacy level, and the decision is left to the prescribing physician	[5,8]
Finland (Fimea)	Allowed under supervision of a health care professional	No comment	[13]
Portugal (Infarmed)	Allowed under supervision of a health care professional	No comment	[13]
Netherland (MEB)	Allowed under supervision of a health care professional	No comment	[14]
France (ANSM)	Not recommended	Allowed when initiating a course of treatment and only if the prescribing physician has not marked the prescription as 'non-substitutable'	[15,16]
Australia (PBAC)	Allowed	Allowed	[17]
Italy (AIFA)	Allowed under supervision of a health care professional	Not recommended	[18]

originator product for the biosimilar in public discussions and publications" [19].

Jointly these statements reflect a paradigm shift in clinical use of biosimilars. Largely the concerns around switching and requirements for data for interchangeability are based on theoretical concerns and aversion to risk rather than on solid facts and data. Professor Kurki has well outlined the science known around biosimilars [88]. In terms of efficacy, it is unlikely that products containing different versions of the same active substance shown to be highly similar on analytical, and clinical pharmacology, efficacy, safety and immunogenicity levels and being comparable at the population level would act differently in an individual patient. Theoretically, differences might occur if the formulations of the biosimilar and the reference product would be very different causing inter-patient variability. This possibility can be clarified by reviewing EPARs of the biosimilars available on the EMA website.

Currently, the main concern of switching patients from a reference product to its biosimilar is immunogenicity. There is no theoretical basis or clinical evidence suggesting that a switch itself would cause immunogenicity. The known examples of switch-related immunogenicity have occurred after a manufacturing process change of an innovator product resulting in an inferior version of the product with altered immunogenicity attributes.

An inferior immunogenicity profile of a biosimilar cannot be completely ruled out but it is unlikely for several reasons. Firstly, high similarity in physicochemical characteristics, and presence of impurities and aggregates provide with assurance of similar immunogenicity; secondly, the ADA responses with biosimilars are always thoroughly investigated before the marketing authorization. Thirdly, the active substance of a biosimilar has the same amino acid sequence as the reference product and, thus, shares the linear T-cell epitopes. A strong immune response would usually require a new T-cell epitope. Some biosimilar developers now also conduct *in vitro* assessment of ELISPOT responses for the comparative immunogenicity purposes. Fourthly, the levels of immunogenic impurities and aggregates are tightly controlled at the release of the biosimilar product. Finally, the knowledge of specific immunological risks with innovator product assists biosimilar developers in developing robust risk management plan and post-marketing pharmacovigilance activities.

In conclusion, the risks of switching to biosimilar products are theoretical and not supported by real world safety experience and extensive use of EU approved biosimilar products for almost 10 years. The science behind development of biosimilars and effective regulatory policies enacted in the EU provide with sufficient assurance of safe and effective switching experiences with biosimilar products. These lessons should be carefully studied and implemented in other jurisdictions where such experience is still relatively limited.

7. Informed decision by patients and prescribers

In line with recommendation of numerous national authorities, patients, pharmacists, physicians, nurses and any other professionals with prescribing powers should be adequately informed about their medication and consulted if any changes in their treatment occur. Patients and prescribers should be able to make an informed decision on merits of switches in terms of their individual benefit-risk considerations. Switching between products should be carried out under supervision and monitoring as this is done with initiation of any biological drug or sequencing of treatment lines. Whilst cost considerations should not be a prime concern for prescribers and patients, economic conditions and tender environment in some jurisdictions and countries can substantially vary influencing the forecast of treatment access. Patients need to be adequately informed if their treatment cannot be assured for appropriate duration of their condition and in such cases patients should be allowed to make informed and balanced decisions on how their condition is managed not only short-term but also from long-term perspective.

8. Cost-effectiveness and switching

In recent years there are now numerous concerns raised by experts over feasibility and adequacy of interchangeability studies with alternate design recommended by FDA. Not only these studies are deemed impractical or scientifically unsound but also with resources, time and effort required for their conduct there might be delay in access of US patients to affordable biosimilar versions. It is therefore thought that interchangeability is an unreachable goal and not so many biosimilar sponsors will opt to conduct complex, large and long-term switching studies in order to fulfill such requirements. Meanwhile, through real-world and pragmatic clinical studies and experiences, the use of biosimilar products in the ex-US territories is rapidly expanding.

The benefits of biosimilar use are expected to translate in earlier access of patients to biological products thus delaying the burden of disease and delaying disease progression. In addition, cost reductions allow release of funding for other healthcare needs. Cost-minimization analyses provide with compelling evidence of cost-effectiveness of biosimilars [89–96].

An important aspect influencing the attitude of physicians towards biosimilars is reimbursement conditions. Physicians are likely to offer patients already on biologic therapy a change to a biosimilar if the patient will benefit from the reimbursement and cost savings, and if this change results in a continuous medicine supply [89–91]. Notably, lack of reimbursement strategies was the main contributor to the slow uptake of biologics in Eastern

European countries and, via the adoption of such strategies, this issue has now been largely addressed.

In the last few years, CT-P13 has been introduced into clinical practice in an increasing number of countries. In Central and Eastern European (where marketing of CT-P13 began in 2014), the introduction of CT-P13 has resulted in a 20–60% reduction in the price of infliximab. Several budget impact analyses have been conducted to evaluate the cost effectiveness that may be associated with switching from originator infliximab to CT-P13 in patients with RA and IBD [89–96]. From May 2015 onwards, patients in Hungary who initiate biologic therapy with infliximab must be treated with CT-P13. In addition, although a mandatory switch to CT-P13 in patients currently treated with RMP infliximab is not recommended, IBD patients in Hungary who relapse more than a year after the previous biologic therapy was stopped should only be treated with the biosimilar [91] In Poland, biologic therapy-naïve patients must be treated with the biosimilar, and patients receiving RMP are mandated to switch to CT-P13 maintenance therapy [91]. Furthermore, National Institute for Health and Care Excellence (NICE) in the UK issued two draft guidances for patients with AS, axial SpA, and UC which cover the use of biosimilars [97,98]. Due to the lower price of CT-P13 compared with RMP, cost savings in the NHS have been projected, depending on final details of the guidance adopted. It is therefore reassuring that two recently issued guidance recommendations by NICE allowed the use of biosimilar infliximab ahead of originator versions in treatment of RA and IBD.

Nevertheless there is still considerable resistance to advent of biosimilars and switching in a number of countries. Policies and regulations obstructing entry of biosimilar products may not only preclude anticipated budget savings and access-related benefits with biosimilars but also may cause public health harms. Firstly latter are linked to opportunity costs resulting from delay of access. Delay or lack of access may cause irreversible end-stage damage or even loss of life (e.g. with oncology biosimilars). Secondly, under tender systems in some countries because of the shortage of funds some healthcare providers are forced to switch patients from biological agents to suboptimal regimens with synthetic DMARDs or steroids whilst these patients are unlikely to benefit from those due to prior failure or lack of tolerance. Finally, the budget savings in specific jurisdictions do not provide with savings that on nationwide scale can assist healthcare to direct these funds in other services and technologies.

Biosimilar development has been set out to accomplish two main goals: reduce the expenditure of healthcare on costly biological treatments and improve patient access to these important and life-changing agents. As we have learned from initially approved EU biosimilars, economically sustainable biosimilar market and sizable impact on healthcare savings can be only accomplished under the following circumstances:

- High quality biosimilar products will be approved under stringent regulatory pathways such as those employed by EMA and more recently by US FDA;
- Switching of biosimilars developed through rigorous comparability exercise and approved in well-regulated jurisdictions should be allowed provided it is carried out carefully and monitored using robust pharmacovigilance tools.

9. Conclusions and recommendations

- Switching between products intended for treatment of autoimmune and oncology disorders is part of medical practice and sequential treatment paradigm;
- Experience with switching and safety of biosimilar products approved in the EU for almost one decade is reassuring and does not raise any concerns regarding effectiveness or safety;
- Observational studies, registries, cohorts and real-world experiences evaluating safety and efficacy upon switching to CT-P13 showed that there are no concerns relating to safety or efficacy in patients with AS, RA and IBD.
- Post-marketing global safety experience with CT-P13 is continuously growing and provides with assurance that switching is both safe and well tolerated.
- Entry of CT-P13 across Europe already provides cost savings and further economic benefits are anticipated as uptake of the product is increasing.

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